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Cardiac Amyloidosis

Amyloidosis is a pathologic and clinical condition resulting from the accumulation of insoluble aggregates of misfolded proteins in tissues. Extracellular deposition of amyloid fibrils in the myocardium leads to cardiac amyloidosis, which is often overlooked as a cause of diastolic heart failure. Although cardiac amyloidosis was previously believed to have a poor prognosis, recent advances in diagnosis and treatment have emphasized the importance of early recognition and changed management of this condition. This article provides an overview of cardiac amyloidosis and summarizes current screening, diagnosis, evaluation, and treatment options.

Screening

Diagnosis

Treatment

Practice Improvement

CME/MOC activity available at Annals.org.

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Amyloid is homogeneous, largely extracellular material that is often identified on a biopsy. It is defined by a specific change in the color of dyes (including Congo red, which has an "apple green" birefringence when viewed via polarizing microscopy) on binding to amyloid deposits. The diagnosis of amyloid disease may be grossly apparent to the pathologist, or it may be identified only with specific stains, immunohistochemistry, or ultrastructural studies.

More than 38 distinct types of amyloid disease have been reported, and each is identified by the amino acid sequence of proteins extracted from amyloid deposits. Insoluble fibrils develop in a stepwise fashion by aggregation into partially folded states, amorphous aggregates, oligomers, protofibrils, and mature fibrils. Nomenclature for the different amyloid proteins includes the designation "A" for amyloid followed by an abbreviation of the unique subunit protein; for example, "AL" means the subunit protein is an immunoglobulin light chain, and "ATTR" means it is transthyretin. These abbreviations may be further modified by whether the subunit protein is normal, which is designated as "wt" for wild-type, or contains a mutation, which is usually a single nucleotide substitution and is designated as "v" for variant, "m" for mutant, or "h" for hereditary.

The diagnosis of systemic amyloidosis may be suggested by distinct presentations. For example, amyloid may be part of the differential diagnosis of proteinuria for a nephrologist, carpal tunnel syndrome for a neurologist or hand surgeon, or restrictive cardiomyopathy (CM) or heart failure with preserved ejection fraction for a cardiologist. Recognizing these presentations facilitates selection of imaging modalities or a biopsy site. Central to the evaluation of a patient with suspected amyloidosis is determining the presence of gammopathy by sending both serum and urine for immunofixation studies and ordering serum free light chain measurements to identify monoclonal immunoglobulin light chains (kappa or lambda) (1, 2).

Once the diagnosis of amyloidosis is confirmed or strongly suspected, the main questions to ask are, "What type of amyloid?" and "Which organs are involved?" Recent progress has been made in diagnosing and treating amyloidosis. We will focus on 2 major forms of amyloid CM, immunoglobulin light chain CM (AL-CM) and transthyretin CM (ATTR-CM), as they are more common and are often overlooked in the clinic.

What is AL amyloidosis?

AL amyloidosis is a systemic disease that affects the heart and other organs. It is rare, with an estimated global prevalence of 8 to 14 people per million per year. The disease is caused by the deposition of immunoglobulin light chains. The normal pool of immunoglobulin light chain reflects multiple antibody specificities, but in AL amyloidosis the immunoglobulin light chain pool is dominated by a single amino acid sequence because of B-cell clonal expansion due to occult or apparent cancer. In addition, about two thirds of the light chain is kappa and about one third is lambda in healthy people, and this ratio is reversed in AL amyloidosis. AL amyloidosis was previously known as "primary amyloidosis."

There is often a long delay between initial symptoms and diagnosis of AL amyloidosis, with rapid clinical progression and high mortality. About 20% to 30% of patients with AL amyloidosis present with congestive heart failure, sometimes advanced, such that the diagnosis may be made only during a terminal hospitalization. Overall, 50% to 70% of patients with AL amyloidosis develop cardiac infiltration, which is sometimes only clinically apparent late in the disease. AL amyloidosis may complicate a spectrum of conditions, including monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, multiple myeloma (about 10% of

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cases), and rarer instances of lymphoma or macroglobulinemia (2).

What is transthyretin amyloidosis?

Transthyretin (TTR) amyloidosis is also a systemic amyloidosis. TTR forms the bulk of the prealbumin band that runs slightly faster than albumin in electrophoresis (hence the "pre-" in "prealbumin"). It is a nonessential transport protein for thyroxine and the major transporter for retinol binding protein and vitamin A, and it is a homotetrameric protein that is a dimer of dimers (3). About 80% to 90% of TTR is synthesized in the liver, with other sites being the retinal pigment epithelium and the choroid plexus (4). Silencing the TTR gene in both mice (5) and humans (6) is well tolerated except for a correctable vitamin A deficiency.

In 1990, TTR was shown to be the subunit of fibrils extracted from amyloid deposits in patients with familial amyloid polyneuropathy (FAP) who formed an endemic focus in northern Portugal. These patients were mostly young adults who developed neuropathy that started in their lower extremities; progressed to their upper extremities; and was followed by muscle wasting, inability to ambulate, inanition, and death. They were heterozygous for a mutation in the TTR gene that led to methionine replacing valine at position 30 (Val30Met). Subsequently, the same TTR abnormality was identified in amyloid from hearts of patients presenting with familial amyloid CM who were mostly in their sixth decade and in an endemic focus in northern Sweden. All the Portuguese patients with this mutation developed polyneuropathy, but a much smaller percentage developed CM, especially female patients. Patients with the Val30Met mutation illustrate the 2 major phenotypes (polyneuropathy and cardiomyopathy) associated with TTR amyloidosis (7, 8). However, more than 135 pathogenic mutations in the TTR gene have been described to date, and these are associated with clinical disease that spans the spectrum from predominant neuropathy to predominant CM (9).

Wild-type TTR amyloidosis (ATTRwt) is an age-related amyloidosis that was previously known as "systemic senile amyloidosis," but this term is no longer used because of its pejorative connotation. The TTR in this form of amyloidosis has a normal amino acid sequence, and the disease predominantly affects older men for unknown reasons (10).

What is the frequency and prognosis of cardiac amyloidosis?

Although several types of amyloid may affect the heart, most cardiac amyloidosis seen in the clinic is due to AL, ATTRv, and ATTRwt systemic amyloidosis. The incidence of each has been increasing in recent years due to greater appreciation of the red flags that trigger diagnostic testing, increased use of diagnostic modalities, and availability of new therapies (11). For example, between 2007 and 2015, the prevalence of AL amyloidosis in the United States increased from 15.5 to 40.5 cases per million, in part from increased testing for immunoglobulin free light chains in serum and urine (12). The worldwide incidence of ATTRv causing FAP has been estimated at 0.3 case per million (5 to 10 000 patients), plus more than 40 000 patients with clinical heart disease who have the Val122Ile mutation (also known as the pVal142Ile mutation), which is prevalent among persons of African American and African Caribbean ancestry (13). In these populations, about 3% of people carry the mutation (14, 15); however, the overall penetrance of Val122Ile in different populations is uncertain and is a subject of study. The frequency of ATTRwt is based mostly on autopsy data. It has been estimated to affect more than 125 000 persons in the United States and possibly 8 million persons worldwide, and that number is projected to increase to 26 million by 2050 (16).

Cardiac involvement is the main determinant of survival in patients with systemic amyloidosis, and it has been reported in up to 90% of patients with AL amyloidosis (17). In contrast, among patients with ATTRv, about 68% have a

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mixed phenotype that includes cardiac amyloid, and about 9% (including Val122Ile) have a cardiac-predominant phenotype (these percentages were calculated from an updated listing of mutations in reference 9). In a retrospective cohort study of 101 patients with biopsy-proven cardiac amyloid, 54% had AL amyloidosis, 42% had TTR amyloidosis, and 5% had unclassified amyloidosis (18). Historically, the average survival after diagnosis was 3.6 years for ATTRwt-CM, 2.6 years for ATTRv-CM with the Val122Ile mutation, and 6 months for AL-CM with severe heart failure (19, 20).

How does the pathophysiology of cardiac amyloidosis relate to clinical presentation?

Amyloid fibrils deposit in the extracellular structures of the heart, which leads to diastolic dysfunction early on and culminates in restrictive CM. Deposition stiffens the myocardial septum and free wall, which leads to increased hemodynamic filling pressures and heart failure. In addition, light chain prefibrils may adversely affect myocyte function by inducing autophagy and proteotoxicity, leading to myocardial oxidative stress early and induction of collagen deposition later in the disease (21). Patients typically present with dyspnea, decreased exercise tolerance, edema, and fatigue. In contrast to hypertensive CM, which predominantly involves the left ventricle, amyloid CM affects both ventricles and the interventricular septum, so some patients present with right heart failure, including ascites, congestive hepatopathy, and even cardiac cirrhosis. Deposition of amyloid in the atria leads to changes in contractility with abnormal sinus node function and abnormal conduction that can produce bradycardia, sick sinus syndrome, heart blocks, palpitations, and syncope. Nonsustained tachycardia is the most common ventricular arrhythmia, though sustained monomorphic or polymorphic tachycardia or fibrillation can occur. Atrial fibrillation is found in up to 70% of patients at diagnosis, often with normal ventricular rates due to conduction disease (22). Elevation in cardiac filling pressures can result in atrial dilatation, and loss of atrial contractility can lead to thrombus formation and embolic stroke, which occur more frequently in patients with cardiac amyloid than in age-matched controls (23). Anginal chest pain may result from comorbid atherosclerotic disease or amyloid involvement of the coronary vasculature (congophilic angiopathy) with impaired vasodilation. Pulmonary hypertension may occur (24, 25). Autonomic dysfunction is common in AL amyloidosis and occurs in about 28% of pathogenic ATTR variants (9) due to infiltration of sympathetic and parasympathetic ganglia, and it can cause postural hypotension and syncope. Minor elevations in cardiac troponins may signify small-vessel occlusion or myofibril deposition, and clinicians can use levels of troponin and *N*-terminal pro–B-type natriuretic peptide (NT-proBNP) to stratify patients according to risk, predict their prognosis, and monitor whether treatment promotes cardiac remodeling (26). Although cardiac amyloid presents as a restrictive CM with preserved systolic function, disease progression with myocyte necrosis and interstitial fibrosis may cause systolic dysfunction (27). The ventricles remain dependent on preload but intolerant to afterload reduction. Therefore, traditional medical therapy for systolic dysfunction, which can decrease preload and afterload, is often not tolerated and may cause harm. Endomyocardial fibril deposition can lead to valvular insufficiency. In addition, several studies describe an association between ATTR-CM and aortic stenosis, although the reasons are unknown (28, 29).

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Which patients should be screened for cardiac amyloidosis?

The general population does not need to be screened for cardiac amyloidosis. However, most clinicians underestimate the prevalence of cardiac amyloid and do not include it in their initial differential diagnosis of hypertensive CM, idiopathic heart failure with preserved ejection fraction, hypertrophic CM, ischemic heart disease, or aortic stenosis. For example, targeted evaluations have found that about 15% of patients who have heart failure with preserved ejection fraction have amyloid (30). Partly as a result, the average delay from symptoms to a correct diagnosis of ATTR-CM ranges from 2 to 4 years (31). Because of these considerations, it may be appropriate to evaluate more patients with these diagnoses for cardiac amyloidosis. In addition, any patient with an established diagnosis of peripheral or autonomic neuropathy caused by amyloid should be evaluated for cardiac involvement (31, 32). Cardiac amyloid should also be considered in patients with carpal tunnel syndrome (33), particularly if it is bilateral or inconsistent with occupational exposure. Finally, cardiac amyloid should be part of the differential diagnosis in patients with ventricular hypertrophy, especially if there is no history of hypertension or valvular heart disease (31) or the electrocardiographic (ECG) voltage is lower than expected when compared with the amount of echocardiographic left ventricular hypertrophy (LVH) (34).

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Table 1. **Red Flag Findings That Should Prompt a Work-up for Cardiac Amyloidosis***

ESC (37, 38)	*DGK (39)*	*CCS/CHFS (40, 41)*	*AHA (42, 43)*	*JCS (44)*
HF at age ≥65 y	Age >60 y, HF symptoms, normal-sized ventricles	Unexplained increased LV wall thickness	Intolerance to antihypertensive or HF medications because of symptomatic hypotension or orthostasis	Symptoms of HF (e.g., shortness of breath, edema), dizziness, and syncope
Aortic stenosis at age ≥65 y	Low voltages or detection of an AV block in the resting ECG	LFLG aortic stenosis with preserved EF (age >60 y)	Neurologic: sensorimotor polyneuropathy (paresthesia and weakness), autonomic dysfunction (orthostatic hypotension, postprandial diarrhea alternating with constipation, gastroparesis, urine retention, and incontinence)	Atrial fibrillation
Hypotension or normotension after previous hypertension	Pericardial effusion, interatrial thickening, granular appearance, RV wall thickening, apical sparing	Carpal tunnel syndrome (bilateral)	Persistent low-level elevation in serum troponin	Conduction system disorder (e.g., AV block, bundle branch block, intraventricular conduction disorder)
Sensory involvement, autonomic dysfunction	Macroglossia with notches in the lateral portion of the tongue	Established AL or ATTR in noncardiac organ/system (i.e., renal AL amyloidosis causing nephrotic syndrome)	Orthopedic: carpal tunnel syndrome, lumbar spinal stenosis, unprovoked biceps tendon rupture, hip and knee arthroplasty	Ventricular arrhythmia
Peripheral neuropathy	Periorbital purpura	Peripheral sensorimotor neuropathy and/or dysautonomia	Discordance between QRS voltage on an ECG and wall thickness on imaging	Low voltage in limb leads
Proteinuria	Atraumatic biceps tendon rupture		Black race	QS pattern in V1-V3
Skin bruising	Sensorimotor polyneuropathy		Unexplained AV block or prior pacemaker implantation	Ventricular wall thickening (including RV)
Bilateral carpal tunnel syndrome	Spinal stenosis		Familial history of polyneuropathy	Atrial septal thickening
Ruptured biceps tendon	Autonomic dysfunction		Unexplained LV wall thickening, RV thickening, or atrial wall thickening	Ventricular diastolic dysfunction (restrictive)
Subendocardial/transmural LGE or increased ECV	Vitreous opacity, pupillary changes		Family history of cardiomyopathy	Granular sparkling appearance
Decreased QRS voltage-to-mass ratio				Pericardial effusion
Pseudo Q waves				Valve thickening
AV conduction disease				Reduction in global longitudinal strain at base of left ventricle (apical sparing)
Possible family history				Elevated BNP and NT-proBNP
				Elevated cardiac troponin T/I
				Global diffuse myocardial LGE in the subendocardial layers on CMR imaging
				Elevated native T1 and ECV fraction in T1 mapping

AHA = American Heart Association; AL = amyloid light chain; ATTR = amyloid transthyretin; AV = atrioventricular; BNP = pro–B-type natriuretic peptide; CCS = Canadian Cardiovascular Society; CHFS = Canadian Heart Failure Society; CMR = cardiac magnetic resonance; DGK = German Cardiac Society; ECG = electrocardiogram; ECV = extracellular volume; EF = ejection fraction; ESC = European Society of Cardiology; HF = heart failure; JCS = Japanese Circulation Society; LFLG = low-flow, low-gradient; LGE = late gadolinium enhancement; LV = left ventricular; MP = monoclonal protein; NT-proBNP = N-terminal pro–B-type natriuretic peptide; RV = right ventricular.
** Adapted from* Journal of the American College of Cardiology, *Vol. 79, Rapezzi C, Aimo A, Serenelli M, et al, Critical comparison of documents from scientific societies on cardiac amyloidosis: JACC state-of-the-art review, 1288-1303, Copyright 2022, with permission from Elsevier.*

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Table 2. **Noncardiac Findings That Should Prompt a Work-up for Amyloidosis in Patients With Heart Failure***

Presentation	*AL Amyloid*	*ATTR Amyloid*
Foamy urine	✓	–
Hepatosplenomegaly	✓	–
Macroglossia	✓	–
Purpura (periorbital, neckline)	✓	–
Arthropathy	✓	–
Skin bruising	✓	–
Autonomic dysfunction (intestinal motility/orthostatic hypotension)	✓	✓†
Dysesthesia	✓	–
Carpal tunnel syndrome (often bilateral)‡	–	✓
Biceps tendon rupture	–	✓
Lumbar spinal stenosis‡	–	✓
Trigger finger‡	–	✓
Vitreous deposits	–	✓
Constipation/diarrhea	✓	✓
Unexplained weight loss (dysphagia, malabsorption)	✓	✓
Polyneuropathy	✓	✓†

AL = amyloid light chain; ATTR = amyloid transthyretin; ATTRv = variant amyloid transthyretin amyloidosis; ATTRwt = wild-type amyloid transthyretin amyloidosis.
** Adapted from Gill SS, Fellin E, Stampke L, et al. Clinical clues and diagnostic workup of cardiac amyloidosis. Methodist DeBakey Cardiovasc J. 2022;18:36-46. doi:10.14797/mdcvj.1061 © 2022 The Authors. Used under CC BY-NC 4.0 license (see https://creativecommons.org/licenses/by-nc/4.0/).*
† More common in this subtype, particularly if hereditary (ATTRv), but also present in ATTRwt.
‡ Bilateral carpal tunnel syndrome, lumbar spinal stenosis, and trigger finger due to amyloid have also been described in systemic AL amyloidosis.

What findings should prompt clinicians to evaluate patients for cardiac amyloidosis?

Cardiac amyloid is frequently misdiagnosed or diagnosed after a substantial delay. On average, patients visit 5 different physicians before the diagnosis is established (35). To avoid this, clinicians should be aware of red flags in a patient's history and physical examination that should prompt consideration of cardiac amyloid (36) (**Table 1**).

Patients are increasingly able to identify family members with amyloidosis, CM, heart failure, sudden death, or pacemaker placement. Therefore, it is important to take a careful and comprehensive family history, particularly in patients of African descent and those from northern Portugal, the Umea region of Sweden, the west coast of Ireland, southern Italy, and other locations with endemic foci of patients with specific ATTR variants (45).

Noncardiac signs and symptoms of cardiac amyloid can be subtle or nonspecific, can involve almost every organ system (46) (**Table 2**), and can precede heart failure by several years. For example, fatigue is reported in more than 80% of patients with cardiac amyloid, and skin bruising may be the only clue to its presence (32, 46). Patients with AL amyloidosis may present with proteinuria and progress to nephrotic syndrome with all its complications. Neurologic conditions that should prompt an evaluation for cardiac amyloid include orthostatic hypotension, other dysfunctions of the autonomic nervous system, dysesthesia, and polyneuropathies such as chronic inflammatory demyelinating polyneuropathy (32, 46). The gastrointestinal (GI) manifestations of amyloid may mimic irritable bowel syndrome (47).

Other conditions that should prompt consideration of AL-CM include a previous diagnosis of gammopathy; macroglossia that may include lateral ridging of the tongue due to indentation by the teeth; "pinch purpura" triggered by minimal trauma over the face and neck; periorbital purpura induced by straining during procedures such as

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proctoscopy; substantial proteinuria; paresthesia; orthostasis; and chronic GI symptoms, including early satiety (17, 19). Conditions that should prompt consideration of ATTR-CM include a history of spinal stenosis (lumbar>cervical with laminectomies typically occurring 8 to 10 years before the diagnosis of ATTR-CM) (48), severe osteoarthritis with joint replacement (typically 5 to 10 years before diagnosis), and biceps tendon rupture (49) or tendinous hypertrophy or contractures. Carpal tunnel syndrome may be an early manifestation of both AL and ATTR amyloidosis, with release procedures often predating recognition of cardiac involvement by 5 to 10 years (50, 51). If tissue has been taken for pathologic examination during a previous surgery or biopsy, the specimen can be examined retrospectively for amyloid. If amyloid is found, the type should be identified using mass spectroscopy, immunostaining, or ultrastructural techniques, depending on available expertise.

Screening... Although the general population need not be screened for cardiac amyloidosis, this condition is often overlooked, so clinicians should have a high index of suspicion for subtle and nonspecific findings in any patient with red flags, and the clinical evaluation should emphasize the patient's history, family history, and review of symptoms, with special attention given to the conditions in **Tables 1** and **2**.

CLINICAL BOTTOM LINE

Diagnosis

No individual laboratory test diagnoses cardiac amyloidosis, but several can be helpful.

How are light chains used to evaluate patients for cardiac amyloidosis?

Measuring monoclonal light chains is a critical first step in the diagnosis of suspected cardiac amyloidosis. Particularly important for the diagnosis of AL amyloidosis is identification of clonal free lambda light chains in serum or urine and a reversal of the normal 2:1 kappa–lambda ratio. Immunofixation electrophoresis of serum and urine is preferred over protein electrophoresis because of higher sensitivity. For example, the combination of serum and urine immunofixation with a serum free light chain assay has sensitivity above 95% for detecting AL amyloidosis (52). Both kappa and lambda light chains may be elevated in the presence of chronic kidney disease due to decreased light chain clearance, but in this situation the normal kappa–lambda ratio is maintained if there is no monoclonal expansion. The diagnosis of AL amyloidosis is complicated when the patient has an MGUS because this can be present in up to 5% of the general population, increases with age, and has been reported in 40% to 50% of patients with ATTRwt and ATTRVal122Ile (53). If abnormal immunofixations or abnormal free light chain ratios are identified, the patient should be referred to a hematologist-oncologist to obtain a bone marrow aspiration and biopsy, flow cytometry, and cytogenetic studies, which can identify clonal plasma cells, amyloid, and translocations that occur more frequently in AL amyloidosis, such as the t(11:14) translocation (2, 19).

BNP and its prohormone (NT-proBNP) are produced by cardiomyocytes in response to increased ventricular stretch. Intermediate NT-proBNP levels can identify early cardiac amyloid in asymptomatic carriers of pathogenic TTR gene mutations and may indicate cardiac involvement in patients with FAP (54). In addition, natriuretic peptides are commonly used longitudinally to measure disease progression and treatment response; however, baseline levels may be

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increased if there is renal disease (55). Cardiac troponins are markers of myocyte damage and may be elevated in cardiac amyloidosis. Because elevated levels of NT-proBNP and troponin I may correlate with cardiac involvement and decreased overall survival, they have been included in widely accepted staging systems for cardiac amyloidosis. Glomerular filtration rate and other parameters may indicate renal involvement and have also been incorporated in risk prediction models (26, 56).

What ECG findings can help identify cardiac amyloidosis?

Discrepancy between the degree of left ventricular wall thickening on echocardiography and QRS voltage on the ECG has historically been accepted as an aid for diagnosis and prognostication (34, 57). However, the prevalence of low QRS voltage depends on the type of amyloid, and thus the absence of this finding is insufficient to rule out a diagnosis (35). Low QRS voltage is found in about 50% of patients with AL amyloidosis and 25% with ATTR amyloidosis (57). A pseudo-infarct Q wave unrelated to a history of myocardial infarction has been reported for 15% to 69% of amyloidosis caused by AL, 18% to 71% caused by ATTRwt, and 18% to 69% caused by ATTRv. The ECG may also find conduction delays and heart block. Any of these findings should prompt further consideration of cardiac amyloidosis, particularly in patients noted to have LVH on cardiac imaging (58).

What role does imaging play in cardiac amyloidosis?

Major modalities include transthoracic echocardiography (TTE), which is often accompanied by myocardial strain imaging if echocardiographic LVH is present; cardiac magnetic resonance (CMR) imaging; and radionuclide imaging. TTE is the primary cardiac imaging modality for the diagnosis of cardiac amyloidosis because it is widely available and provides reliable results. Although echocardiographic findings can be nonspecific, certain features are highly suggestive. Typical findings include increased LV wall thickness greater than 1.2 cm without another explanation for hypertrophy. In addition, patients typically have impaired longitudinal strain with sparing of the apical segments, referred to as a "cherry on top." This finding is specific for ATTR-CM but is not sensitive, so a positive result is more reliable than a negative result, although hypertensive CM may also be accompanied by this finding. Other findings include normal or small LV cavity size, granular speckling myocardium when harmonics are turned off, thickened atrial and interventricular septum, valve thickening, biatrial enlargement, a restrictive diastolic filling pattern, and pericardial effusion (59, 60). The addition of speckle tracking can improve the diagnostic yield of TTE and aid in establishing a prognosis. Transesophageal echocardiography also can detect atrial thrombi and identify patients at risk for embolization if cardioversion is needed for atrial fibrillation (23). Despite these advantages, TTE cannot establish a diagnosis without additional confirmation.

CMR imaging can provide information about myocardial structure and function that complements the TTE, and it can help distinguish amyloid from other hypertrophic conditions (61, 62). Typical CMR findings include diffuse, late, subendocardial gadolinium enhancement that progresses to transmural involvement and is global rather than constrained to the territory of a single epicardial vessel. Also useful are nulling of the myocardium before or simultaneously with blood pooling ("difficulty nulling the myocardium") and increased wall thickness and mass. T1 mapping measures extracellular volume expansion and amyloid deposition, and T2 mapping highlights myocardial edema and inflammation. CMR alone cannot establish a diagnosis of cardiac amyloidosis, although its findings are highly specific (61), and it cannot distinguish between amyloidosis from ATTR versus AL (63). CMR also has a role when results of monoclonal protein tests and radionuclide imaging are negative or

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equivocal and amyloid CM remains in the differential diagnosis, or when echocardiographic imaging is technically difficult. Finally, CMR is being used serially to document regression of cardiac amyloid in patients receiving chemotherapy for AL-CM or tetramer stabilization or silencing therapies for ATTR-CM (62).

Radionuclide imaging can identify specific amyloids, presumably through differential binding to calcium. Quantitative cardiac scintigraphy with ^{99m}technetium pyrophosphate (^{99m}Tc-PYP in the United States and Tc-99m DPD in Europe) compares cardiac uptake to rib uptake at 1 or 3 hours after tracer injection both qualitatively and quantitatively; single-photon emission computed tomography using a gamma camera has the added advantage of facilitating 3-dimensional reconstruction and ensuring that radiotracer is out of the blood pool. For example, in the Perugini grading system, grade 0 indicates no cardiac uptake, grade 1 indicates mild uptake less than the rib, grade 2 indicates moderate uptake equal to the rib, and grade 3 indicates high uptake greater than the rib (64). In the proper clinical context and with a negative evaluation for abnormal light chains, grade 2 or 3 uptake is considered diagnostic of ATTR-CM. However, radionuclide scintigraphy is not perfect. Grade 1 uptake is found in about 40% of patients with AL cardiac amyloidosis. In addition, bone uptake may be seen in areas of increased osteoclast activity associated with osteoarthritis; the wrists and fingers of patients with carpal tunnel syndrome; lumbar stenosis associated with ATTR; and patients with rib fractures, myocardial infarction, and chloroquine-induced CM, thus raising the possibility of false-positive results. Moreover, false-negative results have been reported for some ATTR mutations. In addition, radionuclide imaging can help in the early diagnosis of cardiac amyloidosis in patients with aortic stenosis, diastolic heart failure, carpal tunnel syndrome, or unexplained LVH. As a result, radionuclide scanning has become an established standard in diagnostic algorithms for ATTR cardiac amyloidosis and is now accepted as a substitute for endomyocardial biopsy in appropriate clinical situations, such as once plasma cell dyscrasia has been ruled out (59, 60). Clinicians should be aware that positive technetium-99m imaging results may be associated with other forms of amyloidosis (such as AApoA1) as well as rare cases of chloroquine myotoxicity (65).

When should a biopsy be performed, and how should clinicians choose the site?

Endomyocardial biopsy remains the gold standard for diagnosis and typing of cardiac amyloidosis (18, 66). The American Heart Association suggests that biopsy be considered if there is a positive ^{99m}Tc-PYP scan with evidence of plasma cell dyscrasia, there is a negative or equivocal ^{99m}Tc-PYP scan but clinical suspicion remains high, or a ^{99m}Tc-PYP scan is not available (42). More definitive characterization is obtained by using mass spectroscopy of biopsies to identify the major fibril subunit protein as kappa, lambda, or TTR and to identify sequence abnormalities in ATTRv peptides. Mass spectroscopy has also been used to characterize the proteome associated with amyloid deposition and to identify 2 types of light chain in the same specimen (67, 68) or when multiple types of amyloid coexist.

Though generally safe, endomyocardial biopsy may not be feasible depending on the clinical setting, especially in elderly patients who have higher risks for complications. Alternative biopsy sites include the abdominal fat pad; the minor salivary glands; the stomach, duodenum, and colon; and the prostate and bladder. When polyneuropathy is present, clinicians should consider appropriately selected sites for skin, nerve, or skeletal muscle biopsies. Tissue taken during endoscopies or during surgery of the hand, back, or joints can be examined retrospectively. Moreover, bone marrow biopsies are frequently positive and can also provide useful results. Diagnostic yield varies depending on the site and

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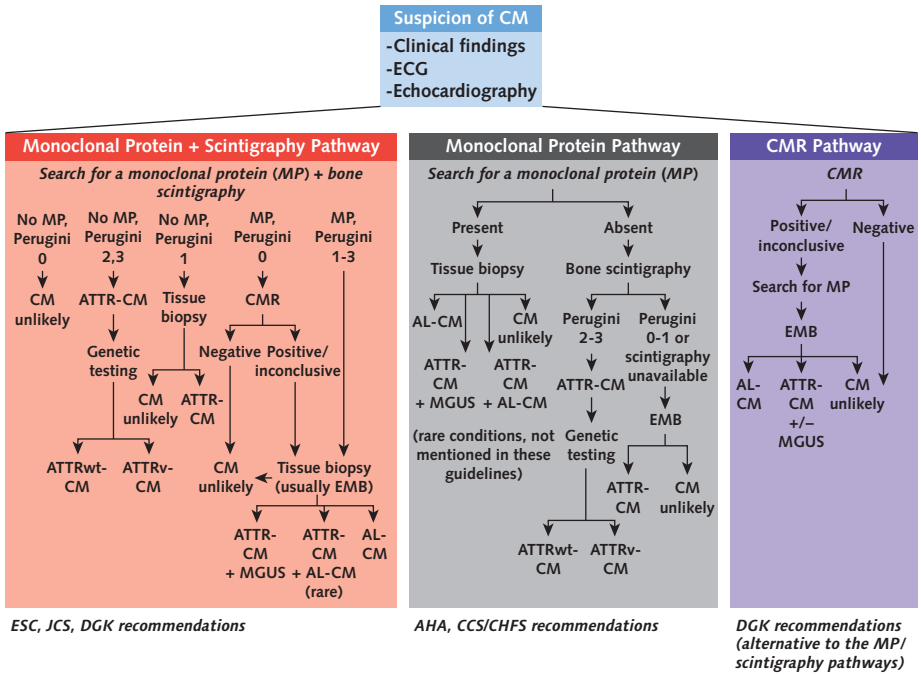
Figure. **Algorithms used to diagnose amyloid CM.**



AHA = American Heart Association; AL-CM = amyloid light chain cardiomyopathy; ATTR-CM = transthyretin cardiomyopathy; ATTRv-CM = variant amyloid transthyretin cardiomyopathy; ATTRwt-CM = wild-type transthyretin cardiomyopathy; CCS = Canadian Cardiovascular Society; CHFS = Canadian Heart Failure Society; CM = cardiomyopathy; CMR = cardiac magnetic resonance; DGK = German Cardiac Society; ECG = electrocardiogram; EMB = endomyocardial biopsy; ESC = European Society of Cardiology; JSC = Japanese Circulation Society; MGUS = monoclonal gammopathy of undetermined significance; MP = monoclonal protein. (Adapted from *Journal of the American College of Cardiology*, Vol. 79, Rapezzi C, Aimo A, Serenelli M, et al, Critical comparison of documents from scientific societies on cardiac amyloidosis: JACC state-of-the-art review, 1288–1303, Copyright 2022, with permission from Elsevier.)

situation, with positive results more likely for AL-CM than for ATTR-CM (69).

Which testing algorithms should be used for the diagnosis of cardiac amyloidosis?

We recommend the diagnostic algorithms from the American Heart Association (42) and the American College of Cardiology (70) (**Figure**).

When should clinicians consider consulting a specialist for diagnosis of patients with possible cardiac amyloidosis?

Once a diagnosis of cardiac amyloidosis is suspected, referral to a cardiologist will facilitate further diagnostic testing and provide access to newer treatments and clinical trials. Patients with cardiac amyloidosis benefit from a multidisciplinary approach that can involve ardiology, hematology-oncology, neurology, gastroenterology, and rheumatology. Referral to a heart failure center should be considered in patients who may require advanced cardiac therapies, such as transplant.

What is the role of genetic testing in patients with cardiac amyloidosis?

Genetic testing can confirm whether ATTR-CM is wild-type or a pathogenic mutation associated more with neuropathy or cardiac disease. However, sporadic cases are frequent among patients from nonendemic areas, and about 9% of known TTR mutations do not cause amyloidosis (9). Patients with a substantial family history of neuropathy, CM, or amyloidosis can be referred to a genetic counselor or an appropriately trained provider who will construct a 3-generation or longer pedigree on the first

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visit and discuss the risks and benefits of genetic testing. Genetic testing may identify TTR mutations that are associated with late-onset disease and may be low-penetrance disorders that overlap with ATTRwt. In addition, ongoing studies are examining early-onset and subclinical disease among populations in whom the Val122Ile mutation is common (13, 71, 72). During a second visit, the counselor usually reviews the genetic testing results and their significance, reviews the clinical histories of first-degree relatives, and discusses the possibility of genetic testing for children older than 18 years to identify at-risk carriers (73).

Diagnosis... Successful diagnosis depends greatly on a heightened suspicion of disease followed by a systematic approach that should include a thorough history, a careful and comprehensive physical examination, appropriate laboratory studies and imaging, and histologic studies when appropriate. Use of a diagnostic algorithm (**Figure**) will facilitate timely evaluations and avoid diagnostic errors. Mass spectroscopy may identify specific mutations by sequence analysis of peptides or be consistent with ATTRwt, which in turn may be further confirmed by a negative genetic test result in an affected person. When genetic testing shows a negative result for ATTRv in a context consistent with ATTRwt, no genetic testing beyond the affected person is necessary. Unaffected family members, including first-degree relatives, should not have genetic testing unless a pathogenic mutation is first identified in the patient or the patient is unavailable for testing.

CLINICAL BOTTOM LINE

Treatment

Current treatments for cardiac amyloidosis focus on the management of heart failure and arrhythmias and strategies to reduce the level of amyloid precursors to slow amyloid deposition. Symptoms of heart failure should be classified according to the New York Heart Association (NYHA) system (70). Also, clinicians should consider using objective measures of functional tolerance, such as the 6-minute walk test and quality-of-life (QOL) inventories (Kansas City Cardiomyopathy Questionnaire [KCCQ] and Minnesota Living With Heart Failure questionnaire [MLWF]). Progression of cardiac amyloid in older patients is significantly influenced by comorbid diseases, such as amyloid neuropathy, diabetes, and atherosclerosis, and these should be included in the overall treatment program.

How should clinicians manage heart failure associated with cardiac amyloidosis?

Patients may be particularly sensitive to fluid and volume shifts and may require a delicate balance between relief of congestion and the need for adequate preload. Loop diuretics may be necessary to maintain euvolemia because of decreased ventricular filling, decreased stroke volume, and elevated filling pressures but should be used with caution. Patients are often intolerant of medications that lower afterload, such as angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. β-Blockers are poorly tolerated due to right ventricular failure and diminished cardiac output. Data are insufficient to support the role of inotropic drugs in cardiac amyloidosis, and digitalis should be used with caution because it binds to amyloid fibrils, which increases its toxicity. Calcium-channel blockers, such as diltiazem and verapamil, should be avoided because of their negative inotropic effects. The role of sodium–glucose cotransporter-2 inhibitors is unknown (35, 42, 70).

How common is atrial fibrillation in cardiac amyloidosis, and which patients should receive systemic anticoagulation?

Atrial fibrillation may be present in as many as 70% of patients, especially in

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those with ATTR amyloidosis. It may precede the diagnosis by several years and may be refractory to medical therapy or ablation (23, 25). All patients with cardiac amyloidosis and atrial fibrillation should receive anticoagulation regardless of their CHA_2DS_2-VASc score because of the high incidence of left atrial thrombus (74).

What treatments are available for patients with AL amyloidosis?

In the past, patients with AL amyloidosis who presented with severe heart failure frequently died during the first 6 months after diagnosis, but average survival is now 5.5 years. The 3 principles for treating patients with AL amyloidosis are early recognition, anti–plasma cell therapy designed to decrease the free light chain level, and supportive care. Cardiac involvement and the stage of disability are the strongest predictors of survival (75, 76), and the success of anti–plasma cell treatment is measured by the completeness of the hematologic response to chemotherapy. The choice of chemotherapy is influenced by the stage of cardiac involvement, as reflected in NT-proBNP and cardiac troponin T levels, and the difference between the levels of kappa and lambda light chains (19, 56). Patients are commonly given combination chemotherapy that includes daratumumab (anti-CD38), bortezomib (proteosome inhibitor), cyclophosphamide, and high-dose dexamethasone (Dara-CyBorD) (77). Patients with refractory or relapsed disease may benefit from other proteosome- or immunomodulator-based treatment, daratumumab, or enrollment in a clinical trial. Patients with advanced heart failure may not tolerate chemotherapy (78). Although autologous stem cell transplant can be considered, fewer than 20% of patients qualify, in part because they tolerate induction agents poorly (79).

What treatments are available for patients with ATTR amyloidosis?

Treatment options include TTR stabilizers, TTR silencers, and TTR disruptors. Stabilizers, which were the first class of medications to be approved by the U. S. Food and Drug Administration (FDA), bind to the tetramer and prevent its dissociation to misfolding monomers. Diflunisal is one of several nonsteroidal anti-inflammatory agents that were found in early drug screens to stabilize the tetramer. In 2013, it was reported to retard the progression of FAP in a controlled multicenter trial involving mostly patients from North America. It was used off label for ATTR amyloidosis in recent studies from Sweden and Australia that reported that it may also halt progression of cardiac amyloidosis and decrease all-cause mortality. However, renal and GI toxicity limit its use, particularly in patients requiring anticoagulation, and it is not available in several countries outside the United States (80).

Tafamidis is an oral small-molecule TTR stabilizer that interacts with the thyroxine binding site. It is FDA-approved for the treatment of wild-type and hereditary ATTR-CM, although its mortality benefits may lag as much as 18 months from the initiation of therapy. Tafamidis at a dose of 20 mg/d was effective in slowing progression of FAP in a controlled trial involving mostly patients with early-onset disease from Portugal (81). This use was extended to patients with ATTR-CM after a randomized controlled trial found it decreased all-cause mortality and cardiovascular hospitalizations after 30 months at doses of 61 and 80 mg/d (82). The trial suggested greater benefit for patients with less advanced disease and little to no effect in NYHA stage 3 or 4 heart disease.

TTR silencers include patisiran and inotersen. Patisiran is a small interfering ribonucleic acid that degrades TTR mRNA in the cytosol, and inotersen is an antisense oligonucleotide that degrades it in the nucleus. Both have been modified to target the liver, where they reduce TTR synthesis, but they also have minimal effects on extrahepatic synthesis in the eye and central nervous system. In a randomized controlled trial, patisiran slowed, and in

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some patients reversed, progression of polyneuropathy and was well tolerated (83). In a cardiac subgroup, patisiran decreased NT-proBNP levels, reduced LVH, slowed the progression of longitudinal strain, and decreased cardiac hospitalizations and all-cause mortality (84). Another randomized controlled trial showed that inotersen also slowed progression of amyloid polyneuropathy and improved QOL compared with placebo (85). Both agents have been FDA-approved for treatment of ATTR neuropathy, and both are undergoing testing for ATTR-CM.

TTR disruptors attempt to eliminate amyloid fibrils from tissues. These agents include doxycycline; TUDCA (tauroursodeoxycholic acid); and nutraceuticals, such as curcumin, resveratrol, and epigallocatechin-3-gallate. Although preclinical trials are promising and the medications are inexpensive, their use has been limited by the availability of stabilizers and silencers (1, 86).

Many consider effective immunotherapy to be the holy grail for advanced amyloidosis because it clears tissue deposits and removes cross-reacting oligomeric precursors from the circulation, particularly for patients with stage 3 and 4 disease. Two antibodies specific for AL light chain conformational determinants (birtamimab and CAEL-101) are being evaluated in patients with AL-CM. In addition, a phase 2 trial is evaluating a novel antibody (NNC6019-0001) that targets misfolded and aggregated forms of ATTR (87, 88).

What is the role of cardiac transplant in patients with cardiac amyloidosis?

Orthotopic heart transplant may be considered for a small subset of patients with isolated cardiac amyloidosis, although most patients will not be candidates because amyloidosis often affects other organs and advanced age is often accompanied by multiple comorbidities. However, 82% of patients who had orthotopic heart transplant between 2010 and 2012 were alive 1 year later, and current guidelines support this option for patients with ATTRwt and those with ATTRVal122Ile. It may also be an option for younger patients with AL amyloidosis and CM before they have chemotherapy or bone marrow transplant if they have minimal extracardiac amyloid (89).

Left ventricular assist devices (LVADs) may be considered for patients sick enough to be considered for heart transplant, but the typical nondilated ventricle of cardiac amyloidosis is incompatible with an LVAD. Although LVADs have been placed in some patients with ATTR cardiac amyloidosis, the device has higher need for biventricular support and carries higher mortality compared with other forms of CM (90). In addition, the prognosis of AL-CM generally precludes benefit from a long-term LVAD.

How should clinicians decide when to refer a patient with cardiac amyloidosis for an implantable cardioverter defibrillator (ICD)?

Whether an ICD can prevent sudden cardiac death in patients with cardiac amyloidosis is unknown. Therefore, decisions about ICDs in these patients should be individualized and weighed against the overall prognosis (91, 92).

How should clinicians monitor patients with cardiac amyloidosis?

Consensus recommendations for monitoring patients with cardiac amyloidosis highlight 3 ways to measure disease progression: clinical evaluation and QOL measures of daily function, biomarkers, and ECGs and imaging studies. Clinical parameters include frequency of hospitalizations for heart failure or a change in NYHA class, 6-minute walk distance, or KCCQ score. Biomarkers include a 30% increase in NT-proBNP or troponin level, and imaging changes include an increase in LV thickness or grade of diastolic dysfunction, changes in strain, or new-onset conduction disturbance. One marker from each domain is required to determine progression of ATTR-CM. Measures should be assessed at baseline and every 6 to 12 months (depending on the measure) (93). Data on monitoring for disease progression and response to therapy remain limited (94).

When should patients with cardiac amyloidosis be hospitalized?

There is no consensus about the criteria for hospitalization. Most hospitalizations in patients with cardiac amyloidosis are for acute decompensated heart failure or unstable arrhythmias and often involve issues related to treatment changes.

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Treatment... Treatment for cardiac amyloidosis focuses on the management of heart failure and arrhythmias and strategies to slow amyloid deposition. Patients with cardiac amyloidosis do not tolerate many of the medications commonly used to treat heart failure in patients with other causes, particularly when systolic dysfunction develops. Atrial fibrillation eventually develops in most patients, and all patients without contraindications should receive anticoagulation regardless of their CHA_2DS_2-VASc score. Patients with AL cardiac amyloidosis who need specific treatment should be started on combination chemotherapy. Most patients with ATTR cardiac amyloidosis who need drug therapy should be considered for tafamidis unless end-stage heart failure is present. For patients with advanced disease, cardiac transplant may be considered, but eligibility may be limited by comorbidities and end-organ dysfunction. Whether an ICD can effectively prevent sudden cardiac death is unknown. Early evidence suggests that new treatments for cardiac amyloidosis may slow disease progression and improve longevity.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend regarding the care of patients with amyloidosis?

In the past 7 years, 5 national and international societies have issued documents on cardiac amyloidosis (36, 70). All include similar diagnostic algorithms that emphasize the importance of clinical suspicion, red flags, and early diagnosis, and all describe a diagnostic approach that begins with imaging. They differ only in whether to begin with measuring monoclonal protein followed by radionuclide imaging versus measuring monoclonal protein and doing radionuclide imaging simultaneously versus CMR imaging. All emphasize that a histologic diagnosis is necessary to diagnose AL amyloidosis and may be necessary for ATTR amyloidosis when other modalities show negative or equivocal results but clinical suspicion is high or when multiple forms of amyloidosis remain in the differential diagnosis (36) (**Figure**).

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In the Clinic
Tool Kit

Cardiac Amyloidosis

Patient Information

https://medlineplus.gov/amyloidosis.html
Information and handouts on amyloidosis from the National Institutes of Health's MedlinePlus.

www.heart.org/en/health-topics/cardiomyopathy/what-is-cardiomyopathy-in-adults/transthyretin-amyloid-cardiomyopathy-attr-cm
Information on transthyretin amyloid cardiomyopathy from the American Heart Association.

www.cancer.net/cancer-types/amyloidosis
Patient guide on amyloidosis from the American Society of Clinical Oncology.

Information for Health Professionals

https://academic.oup.com/eurheartj/article/42/16/1554/6212698
Position statement from the European Society of Cardiology Working Group on the diagnosis and treatment of cardiac amyloidosis.

www.onlinecjc.ca/article/S0828-282X(20)30042-8/fulltext
Joint position statement from the Canadian Cardiovascular Society and the Canadian Heart Failure Society on the evaluation and management of patients with cardiac amyloidosis.

www.ahajournals.org/doi/10.1161/CIR.0000000000000792
Scientific statement from the American Heart Association on the evolving diagnosis and management of cardiac amyloidosis.

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WHAT YOU SHOULD KNOW ABOUT CARDIAC AMYLOIDOSIS

What Is Cardiac Amyloidosis?

Amyloidosis is a group of rare diseases. These diseases occur when the body produces a protein called amyloid that is deposited in the body. Deposits can concentrate in the heart, nerves, kidneys, gastrointestinal tract, or other places. In some patients, amyloid affects mostly 1 organ, but in other patients, it affects several organs. Amyloid deposits can interfere with how an organ works, and symptoms depend on which organs are involved. When amyloid deposits in the heart, it can cause weakness, tiredness, shortness of breath, swelling of the ankles and legs, and other symptoms of heart failure. Some types of amyloid occur in families, but others do not. Symptoms from amyloid may begin at any time during a person's life but are more common in older people.

What Are the Risk Factors?

Amyloid occurs with some types of blood cancer or when there is chronic inflammation from infection or autoimmune disease. Some patients have gene mutations. However, many patients with amyloidosis do not have any of these problems.

Who Should Be Screened?

People in the general population do not need to be screened for cardiac amyloidosis. However, the possibility of cardiac amyloidosis should be investigated in patients with certain types of heart failure and some other heart problems, especially when these patients do not have other explanations for their conditions.

How Is It Diagnosed?

Different types of information are important, and no single type of information is sufficient. A diagnosis of cardiac amyloidosis requires information about your own medical history, the medical

histories of your close relatives, a physical examination, blood tests, and images of your heart. Sometimes a biopsy is required, and gene testing may be useful.

How Is It Treated?

The goals of treatment are to control the symptoms of heart failure, prevent the complications of abnormal heart rhythms, and slow amyloid deposition. Medications are available to help achieve these goals. However, the medications that control symptoms and prevent complications need to be used differently in patients with cardiac amyloidosis than in patients with other causes of heart failure. Also, specific medications are available to slow amyloid deposition, but different types of medications are used for different types of cardiac amyloidosis.

Questions for My Doctor

- Does my treatment have side effects?
- How long will it take for me to feel better?
- What additional treatments are available?
- How often should I return for monitoring of my condition?
- What symptoms require emergency care?
- Are there any activities I should avoid?
- How long will I have to take my medications?

For More Information

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MedlinePlus
https://medlineplus.gov/amyloidosis.html

Mayo Clinic
www.mayoclinic.org/diseases-conditions/amyloidosis

Johns Hopkins Medicine
www.hopkinsmedicine.org/health/conditions-and-diseases/amyloidosis

Cleveland Clinic
https://my.clevelandclinic.org/health/diseases/23398-amyloidosis

Patient Information

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